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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	20.01.2005
Applicant's or agent's file reference -002555-0011 9832-006	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA 03/01418	17.09.2003	18.09.2002

Applicant
CENTRE HOSPITALIER DE L'UNIVERSITE DE MONTREAL ...

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

   The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

   Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

   For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

   The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	de Haas, B Tel. +31 70 340-4738

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

REC'D 20 JAN 2005

INTERNATIONAL PRELIMINARY EXAMINATION REPORT PCT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 002555-0011	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/CA 03/01418	International filing date *(day/month/year)* 17.09.2003	Priority date *(day/month/year)* 18.09.2002
International Patent Classification (IPC) or both national classification and IPC C12N15/16		
Applicant CENTRE HOSPITALIER DE L'UNIVERSITE DE MONTREAL ...		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.04.2004	20.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Macchia, G Telephone No. +31 70 340-4078

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA 03/01418

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-11, 13, 15-32	as originally filed
12, 14	received on 27.12.2004 with letter of 23.12.2004

Sequence listings part of the description, Pages

1-57	received on 26.07.2004 with letter of 23.07.2004

Claims, Numbers

1-16	as originally filed
17-38	received on 27.12.2004 with letter of 23.12.2004

Drawings, Sheets

1/3-3/3	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 10, 14-16, 36-38, with respect to industrial applicability,

because:

☒ the said international application, or the said claims Nos. 10, 14-16, 36-38, with respect to industrial applicability, relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	22-38
	No:	Claims	1-21
Inventive step (IS)	Yes:	Claims	22-38
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-9, 11-13, 17-35

No: Claims

2. Citations and explanations

see separate sheet

Reference is made to the following document:

D1: US-A-5 854 216 (GAUDREAU Pierrette; UNIVERSITÉ DE MONTREAL) 29 December 1998.

Re Item I
Basis of the Report

I.1). The amendments provided by the Applicant on pages 12 and 14 are acknowledged within the meaning of Rule 91 PCT.

I.2). Present claims 17-38 are considered as meeting the requirements of Article 34(2)(b) PCT, see however the remarks concerning claim 36 under following point V.7).

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1). Claims **10**, **14-16** and **36-38** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1). Document D1 discloses GHRH analogues falling within the terms of claims 1-21, and their use as markers (D1: tables 10-12 and relevant parts throughout the entire document).

The subject-matter of claims **1-21** is therefore not novel (Article 33(2) PCT).

The ISA acknowledges that D1 does not disclose a therapeutic utility of the GHRH

analogues disclosed in this document. However, the wording of present claims 1-21 does not allow to distinguish their subject-matter from the disclosure of D1.

V.2). Present claims **22-38** meet the requirements of Article 33(2) PCT because their subject-matter was not disclosed in the available prior art.

V.3). The document D1 is regarded as being the closest prior art and discloses GHRH analogues, as already commented under previous point V.1).

The subject-matter of claims 22-38 differs from the disclosure of D1 in that pharmaceutical compositions comprising GHRH analogues and related uses are concerned.

The problem to be solved by the present invention may therefore be regarded as the provision of a further application of GHRH analogues.

The solution proposed in claim **22-38** of the present application can be considered as involving an inventive step (Article 33(3) PCT) because D1 discloses GHRH analogues which show various *in vitro* affinity for a rat growth hormone receptor. These affinity data on a rat receptor is not predictive of affinity for a human receptor, as shown by the Applicant in Table 1 of present application.
In this respect, D1 does not show the affinity of the GHRH analogues disclosed for a human growth hormone receptor, neither it shows that these compounds are resistant to proteolysis nor that they are able to increase growth hormone levels in a mammal (*in vivo*).

Therefore, it should be concluded that a possible therapeutical application of the GHRH analogues of D1 is not suggested and cannot be deduced from the disclosure of D1.

Consequently, the person skilled in the art should have made use of inventive skills in order to derive a possible utility of the compounds claimed in therapy.

V.4). The industrial applicability of the subject-matter of claims **1-9, 11-13** and **17-35** is acknowledged (Article 33(4) PCT).

V.5). For the assessment of the present claims **10, 14-16** and **36-38** on the question whether they are industrially applicable, no unified criteria exist in the

PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

In addition to the comments above, the following issues do not meet the requirement of Article 6 PCT.

V.6). In the claims, it is referred to a " functional derivative " of the GHRH analogues disclosed in present application, without giving a true technical characterization of said derivative.
As a matter of fact, on page 7 present application tries to define said functional derivative in terms of structure and function. However, present application does not indicate any true technical feature associated with said term, enabling the person skilled in the art to identify unambiguously the subject-matter concerned.

Therefore the application does not meet the requirements of Article 5 PCT, because said functional derivatives are not sufficiently disclosed.

In addition to this, the application does not meet the requirements of Article 6 PCT because the term " functional derivative " is not sufficiently supported, is not characterized by true technical features and is open to interpretation.

V.7). In present claim 36, it is not clear whether the term " wherein said analogue comprises at least one amino acid substitution in the native form of hGHRH1-29 " should be interpreted as:

(1) wherein said analogue comprises at least one amino acid substitution **in the residues mentioned (A2, A8, A10, A15, A30);**

or

(2) wherein said analogue comprises at least one amino acid substitution **in addition to the modifications in the residues mentioned (A2, A8, A10, A15, A30).**

Therefore the wording of the claim is such as to render the matter for which protection is sought unclear (Article 6 PCT).
Moreover, should the wording of the claim be interpreted according to version (2), its subject-matter would not even meet the requirements of Article 34(2)(b) PCT.

hGHRH(1-29)- NH_2, for: i- their increased relative binding affinity to hGHRH(1-44)- NH_2 binding sites in rat anterior pituitary *in vitro* as well as to hGHRH-R in BHK-expressing cells *in vitro*; and ii- their relative resistance to proteolysis *in vitro*.

As can be noted from Table 1 below, the relative binding affinity of the synthetic peptides with the rat GHRH receptor is not predictive of the relative binding affinity with the human receptor. As will be noted, from this point forward, GHRH analogues as presented in Table 1 will be referred to as GHRH analogues # 1 to 5.

Table 1. Priority selection based on the expected theoretical combined effects of receptor affinity and *in vitro* resistance to proteolysis on the overall bioactivity of GHRH analogues in rat anterior pituitary membrane preparations and rat serum, respectively, and of receptor affinity in BHK cell membrane preparations.

No.	Structure	Relative binding affinity in rat anterior pituitary*†	Relative binding affinity in hGHRH-R BHK-expressing cells*†	Relative resistance to proteolysis *in vitro*
1	[D-Ala^2, Ala^8, Ala^{15}, Lys^{22}] hGHRH(1-29)- NH_2	13.33 ± 0.31	499 ± 234	1.87
2	[Ala^8, Ala^9, Ala^{15}, Ala^{22}] hGHRH(1-29)- NH_2	7.74 ± 3.49	3.70 ± 0.52	1.81
3	[D-Ala^2, D-Tyr^{10}, Lys^{22}] hGHRH(1-29)- NH_2	4.90 ± 2.70	239 ± 55	2.25
4	[D-Ala^2, Ala^8, D-Tyr^{10}, Ala^{15}, D-Lys^{21}, Lys^{22}] hGHRH(1-29)- NH_2	5.00 ± 0.91	0.05 ± 0.01	6.06
5	[D-Ala^2, D-Tyr^{10}D−Ala^{15}, Lys^{22}] hGHRH(1-29)- NH_2	1.04 ± 0.40	939 ± 249	3.13

GHRH analogue numbers in Table 1 correspond to numbers 13, 11, 7, 14 and 8 in Table 11 on pages 27-28 of the US patent No. 5,854,216, respectively. *, values compared to hGHRH(1-29)-NH_2; †, use of [^{125}I-Tyr^{10}]hGHRH(1-44)-NH_2 as a radioligand in structure-affinity studies.

EXAMPLE 2

Processing of the native GHRH and GHRH analogues of the present invention – Experimental assays

1- Competitive binding assay

^{125}I-GHRH binding assay was performed as previously described (Boulanger L, *et al.* (1999) Neuroendocrinology 70 : 117-127), using [^{125}I-Tyr^{10}]hGHRH(1-44)NH_2 as radioligand. Competition experiments were done in BHK (baby hamster kidney) 570

binary solvent system composed of NaClO4 0.01 M, pH 2.5 and acetonitrile. A linear gradient from 30 to 60 % acetonitrile over 45 min (rat serum) or 30 to 50% (human serum and plasma) was used. Elution of intact peptide was monitored at 214 nm and residual concentration determined by assessment of peak surface areas (Boulanger L, *et al.* (1993) Brain Res 616: 39-47; Boulanger L, *et al.* (1992) Peptides 13: 681-689).

3- *In vivo* administration of native GHRH or GHRH analogue

The ability of human GHRH analogue # 5 (human [D-Ala^2, D-Tyr^{10}D-Ala^{15}, Lys^{22}] GHRH (1-29)NH_2 analogue) to stimulate GH secretion was studied in adult female rats (26-34 weeks at onset of treatment) and in a male Beagle dog.

i – *In vivo* administration into rats

Human GHRH analogue # 5 in 0.9% sodium chloride for injection USP was administered once either by intravenous (IV) or subcutaneous (SC) injection to female rats followed by a 14-day observation period, as shown in Table 2. Prior to administration, all dosing formulations were filtered using a 0.22 µm filter to ensure sterility. The actual amount of GHRH analogue # 5 administered was calculated and adjusted based on the animal's most recent body weight. Dosing started at approximately the same time each day, commencing at 9:00 am ± 30 minutes.

17. A GHRH analogue or a pharmaceutically acceptable salt thereof able to stimulate secretion or synthesis of growth hormone in a mammal, said GHRH analog or pharmaceutically acceptable salt having an *in vitro* potency index substantially higher than the *in vitro* potency index of a native hGHRH1-29 and having formula Tyr- D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Asn- Ser-D-Tyr^{10}-Arg-Lys-Val-Leu- D-Ala^{15}-Gln-Leu-Ser-Ala-Arg-Lys-Lys^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-A30-NH_2, wherein A30 is a bond or any amino acid sequence of 1 up to 15 residues.

18. A GHRH analogue according to claim 17, wherein the *in vitro* potency index is at least 500-fold higher than the *in vitro* potency index of a native hGHRH1-29.

19. The GHRH analogue of claim 18, wherein the *in vitro* potency index is at least 1500-fold higher than the *in vitro* potency index of a native hGHRH1-29.

20. The GHRH analogue of claim 19, wherein the *in vitro* potency index is at least 2500-fold higher than the *in vitro* potency index of a native hGHRH1-29.

21. The GHRH analogue of claim 17, wherein said GHRH analogue has the formula Tyr- D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Asn- Ser-D-Tyr^{10}-Arg-Lys-Val-Leu- D-Ala^{15}-Gln-Leu-Ser-Ala-Arg-Lys-Lys^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg -NH_2

22. A pharmaceutical composition, comprising:

a) an effective amount of a GHRH analogue or a pharmaceutically acceptable salt thereof comprising formula X:Tyr-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-A10-Arg-Lys-Val-Leu-A15-Gln-Leu-Ser-Ala-Arg-Lys-A22-Leu-Gln-Asp-Ile-Met-Ser-Arg-A30-NH_2, wherein
A2 is Ala or D-Ala;
A8 is Asn, D-Asn or Ala;
A10 is Tyr or D-Tyr;
A15 is Gly, Ala or D-Ala;
A22 is Leu, D-Leu, Lys or Ala; and
A30 is a bond or any amino acid sequence of 1 up to 15 residues and wherein said analogue comprises at least one amino acid substitution in the native form of hGHRH1-29; and;

b) a pharmaceutically acceptable carrier.

23. The pharmaceutical composition of claim 22, wherein said GHRH analogue or salt thereof is selected from the group consisting of, and wherein:

- A2 is D-Ala, A8 is Ala, A15 is Ala, A22 is Lys;
- A2 is D-Ala, A10 is D-Tyr, and A22 is Lys and;
-A2 is D-Ala, A10 is D-Tyr, A15 is D-Ala, and A22 is Lys.

24. The pharmaceutical composition of claim 23, wherein A2 is D-Ala, A8 is Asn, A10 is D-Tyr, A15 is D-Ala, A22 is Lys and A30 is a bond.

25. A pharmaceutical composition, comprising:

a) an effective amount of a GHRH analogue or a pharmaceutically acceptable salt thereof of formula X:Tyr-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-A10-Arg-Lys-Val-Leu-A15-Gln-Leu-Ser-Ala-Arg-Lys-A22-Leu-Gln-Asp-Ile-Met-Ser-Arg-A30-NH_2, wherein
A2 is Ala or D-Ala;
A8 is Asn, D-Asn or Ala;
A10 is Tyr or D-Tyr;
A15 is Gly, Ala or D-Ala;
A22 is Leu, D-Leu, Lys or Ala; and
A30 is a bond or any amino acid sequence of 1 up to 15 residues and wherein said analogue comprises at least one amino acid substitution in the native form of hGHRH1-29; and;

b) a pharmaceutically acceptable carrier.

26. The pharmaceutical composition of claim 25, wherein said GHRH analogue or salt thereof is selected from the group consisting of, and wherein:

- A2 is D-Ala, A8 is Ala, A15 is Ala, A22 is Lys;
- A2 is D-Ala, A10 is D-Tyr, and A22 is Lys and;
-A2 is D-Ala, A10 is D-Tyr, A15 is D-Ala, and A22 is Lys.

27. The pharmaceutical composition of claim 26, wherein A2 is D-Ala, A8 is Asn, A10 is D-Tyr, A15 is D-Ala, A22 is Lys and A30 is a bond.

28. A pharmaceutical composition for stimulating secretion or synthesis of growth hormone in a mammal in need thereof, the pharmaceutical composition comprising:

a) an effective amount of a GHRH analogue or a pharmaceutically acceptable salt thereof comprising formula X:Tyr-A2-Asp-Ala-Ile-Phe-

Thr-A8-Ser-A10-Arg-Lys-Val-Leu-A15-Gln-Leu-Ser-Ala-Arg-Lys-A22-Leu-Gln-Asp-Ile-Met-Ser-Arg-A30-NH_2 , wherein

A2 is Ala or D-Ala;

A8 is Asn, D-Asn or Ala;

A10 is Tyr or D-Tyr;

A15 is Gly, Ala or D-Ala;

A22 is Leu, D-Leu, Lys or Ala; and

A30 is a bond or any amino acid sequence of 1 up to 15 residues and wherein said analogue comprises at least one amino acid substitution in the native form of hGHRH1-29, and;

b) a pharmaceutically acceptable carrier.

29. The pharmaceutical composition of claim 28, wherein said GHRH analogue or salt thereof is selected from the group consisting of, and wherein:

- A2 is D-Ala, A8 is Ala, A15 is Ala, A22 is Lys;
- A2 is D-Ala, A10 is D-Tyr, and A22 is Lys and;
-A2 is D-Ala, A10 is D-Tyr, A15 is D-Ala, and A22 is Lys.

30. The pharmaceutical composition of claim 29, wherein A2 is D-Ala, A8 is Asn, A10 is D-Tyr, A15 is D-Ala, A22 is Lys and A30 is a bond.

31. The use of a GHRH analogue, or a pharmaceutically acceptable salt thereof in the preparation of a pharmaceutical composition for stimulating secretion or synthesis of growth hormone in a mammal in need thereof, said GHRH analog or pharmaceutically acceptable salt comprising formula X: Tyr-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-A10-Arg-Lys-Val-Leu-A15-Gln-Leu-Ser-Ala-Arg-Lys-A22-Leu-Gln-Asp-Ile-Met-Ser-Arg-A30-NH_2, wherein

A2 is Ala or D-Ala;

A8 is Asn, D-Asn or Ala;

A10 is Tyr or D-Tyr;

A15 is Gly, Ala or D-Ala;

A22 is Leu, D-Leu, Lys or Ala; and

A30 is a bond or any amino acid sequence of 1 up to 15 residues and wherein said analogue comprises at least one amino acid substitution in the native form of hGHRH1-29.

37. The use according to claim 36, wherein said mammal has a disorder selected from the group consisting of hypothalamic pituitary dwarfism, burns, osteoporosis, renal failure, non-union bone-fracture, acute/chronic debilitating illness or infection, wound healing, reduction of the incidence of post-surgical problems, lactation failure, infertility in women, cachexia in cancer patients, anabolic and/or catabolic problems, T-cell immunodeficiencies, neurodegenerative conditions, GHRH receptor-dependent tumors, aging, sleep disorders, muscle wasting diseases such as in sarcopenic patients, frail elderlies, HIV patients and cancer patients having radiotherapy and chemotherapy side-effects.

38. The use according to claim 37, wherein said muscle wasting diseases are selected from the group consisting of; sarcopenia, frailty in elderlies, HIV and cancer.

32. The use as defined in claim 31, wherein said GHRH analogue or salt thereof is selected from the group consisting of, and wherein:

- A2 is D-Ala, A8 is Ala, A15 is Ala, A22 is Lys;
- A2 is D-Ala, A10 is D-Tyr, and A22 is Lys and;
- A2 is D-Ala, A10 is D-Tyr, A15 is D-Ala, and A22 is Lys.

33. The use as defined in claim 32, wherein A2 is D-Ala, A8 is Asn, A10 is D-Tyr, A15 is D-Ala, A22 is Lys and A30 is a bond.

34. The use according to claim 31, wherein said mammal has a disorder selected from the group consisting of hypothalamic pituitary dwarfism, burns, osteoporosis, renal failure, non-union bone-fracture, acute/chronic debilitating illness or infection, wound healing, reduction of the incidence of post-surgical problems, lactation failure, infertility in women, cachexia in cancer patients, anabolic and/or catabolic problems, T-cell immunodeficiencies, neurodegenerative conditions, GHRH receptor-dependent tumors, aging, sleep disorders, muscle wasting diseases such as in sarcopenic patients, frail elderlies, HIV patients and cancer patients having radiotherapy and chemotherapy side-effects.

35. The use according to claim 34, wherein said muscle wasting diseases are selected from the group consisting of; sarcopenia, frailty in elderlies, HIV and cancer.

36. The use of a GHRH analogue, or a pharmaceutically acceptable salt thereof for stimulating secretion or synthesis of growth hormone in a mammal in need thereof, said GHRH analog or pharmaceutically acceptable salt comprising formula X: Tyr-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-A10-Arg-Lys-Val-Leu-A15-Gln-Leu-Ser-Ala-Arg-Lys-A22-Leu-Gln-Asp-Ile-Met-Ser-Arg-A30-NH_2, wherein

A2 is Ala or D-Ala;
A8 is Asn, D-Asn or Ala;
A10 is Tyr or D-Tyr;
A15 is Gly, Ala or D-Ala;
A22 is Leu, D-Leu, Lys or Ala; and
A30 is a bond or any amino acid sequence of 1 up to 15 residues and

wherein said analogue comprises at least one amino acid substitution in the native form of hGHRH1-29.